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Radiographic joint space width is correlated with 4-year clinical outcomes in patients with knee osteoarthritis: data from the osteoarthritis initiative

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SUMMARY

Objective: To evaluate if quantitative joint space width (JSW) measurements from radiographs correlate with 4-year Knee injury and Osteoarthritis Outcome Scores (KOOS) and clinical performance measures.
Method: The study group consisted of 942 patients with symptomatic knee osteoarthritis (OA). 4-year outcomes for six measures (KOOS Pain, Symptom, Quality of Life, and Function scores, 20-m walk pace, and chair stand time) were used to create six multiple linear regression models. Primary predictors were baseline minimum JSW and 4-year change in JSW measured from fixed flexion radiographs. Age, gender, body mass index (BMI), race, knee alignment, and baseline measures of the outcomes of interest were covariates.
Results: Lower baseline minimum JSW and a greater decrease in 4-year JSW significantly correlated with worse 4-year KOOS Pain, Symptom, and Quality of Life. With all other factors constant, a 4.1, 4.8, and 5.6 mm lower baseline JSW correlated with a clinically significant eight-point drop in 4-year KOOS Pain, Symptom, and Quality of Life scores respectively. Additionally, a 3.5, 3.1, and 4.0 mm loss of JSW over 4 years correlated with a clinically significant eight-point drop in 4-year KOOS Pain, Symptom, and Quality of Life scores respectively.
Conclusions: Our results indicate quantitative radiographic JSW measurements correlate with 4-year clinical outcomes. Since patients with narrower JSW at the onset of study had lower KOOS scores at 4 years even after controlling for 4-year change in JSW and baseline KOOS scores, clinical outcomes in knee OA may be predetermined once the disease process begins. These findings suggest early treatment with disease modifying therapies may be necessary to influence outcomes.

Introduction

Osteoarthritis (OA) is one of the most common causes of disability in the United States and presents a large burden on individuals and the healthcare system. The knee is one of the most common joints affected by OA with an estimated prevalence in adults over 45 of 19.2% and 27.8% in the Framingham Study and Johnson County Osteoarthritis Project, respectively[1]. The prevalence is expected to grow in the coming years as a result of an aging population. Furthermore, the lifetime risk of having symptomatic knee OA is estimated to be 45% for the general population and 61% among obese individuals[2]. In terms of healthcare utilization, patients with knee OA have been shown to have significantly more doctor's visits and hospitalizations than patients without knee OA[3]. In 2009, one study estimated over 600,000 hospital discharges in the US as a result of knee OA costing $28.5 billion[4].

The pathogenesis of knee OA involves articular cartilage degradation, inflammation of synovial tissues, and changes in subchondral bone[5]. As a standard measure of anatomical disease progression, joint space width (JSW) is the distance measured between the femoral condyle and tibial plateau on radiographs obtained in a standardized fashion. Articular cartilage loss is indirectly inferred based on loss of JSW and referred to as joint space narrowing (JSN)[6]. Magnetic resonance imaging (MRI) has proved to be a very sensitive technique to evaluate the status of most knee

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structures including cartilage, meniscus, bone, and ligaments. However, despite the advances in MRI and quantitative image analysis techniques, radiographic JSN is currently the biomarker accepted by the United States Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA) as an end point in clinical trials for measurement of OA progression[6].

JSN measurements are appropriate to estimate structural disease progression, but they do not directly evaluate the impact of knee OA on patients' lives. The Knee injury and Osteoarthritis Outcome Score (KOOS) is a validated and reliable patient-reported outcome measure evaluating pain, symptoms, function, and quality of life[7]. Other objective performance tests, including 20-m walk pace and time to perform five chair stands, can also be used to measure patients' abilities[8]. These clinical measurements are suitable to evaluate the progression of knee OA as experienced by the patient.

Although a relationship between radiographic and clinical knee OA progression would be anticipated, evidence to date has not established a strong correlation. A systematic search of the literature by Bedson and Croft in 2008 concluded that radiographic changes in knee OA were an imprecise marker of knee pain[9]. They concluded the discordance was caused by variations in X-ray views, X-ray grading, pain definition, and study population. A systematic review conducted in 2011 supported the discordance and found only 10% of reviewed studies associated radiographic and clinical OA features[10].

The Osteoarthritis Initiative (OAI) is a longitudinal, multicenter, prospective, observational cohort study of knee OA. A publically available database has been established containing yearly clinical assessments, biospecimens, MRI, X-ray, and outcome data from patients with symptomatic OA or at elevated risk of OA[11]. Over 4,700 patients ages 45–79 were enrolled between February 2004 and May 2006. This database provides a valuable opportunity to follow a large, nationwide patient group. In this study, we evaluate the association of radiographic disease state and clinical outcome measures in a cohort of OAI patients. We hypothesize that JSN over 4 years would be associated with worsening clinical outcomes after adjusting for demographic factors, baseline JSW, and baseline clinical scores.

Methods

Study population

Data used in the preparation of this article were obtained from the OAI database, which is available for public access at http://www.oai.ucsf.edu/. Specific datasets used were AllClinical 0.2.2 and 6.2.1 and kXR quantJSW 0.5 and 6.2. Patients for the current study were derived from the progression subcohort. Inclusion into this subcohort was based on having both of following criteria in at least one knee at enrollment: "pain, aching, or stiffness in or around the knee on most days" for at least 1 month in the past 12 and definite tibiofemoral osteophytes (Osteoarthritis Research Society International atlas grades 1–3 or Kellgren and Lawrence grade $\geq$2) on the fixed flexion radiograph. With these criteria, we identified 1,278 patients of which 942 had complete data for all variables of interest and were included in our analyses. The patient's right knee was chosen as the unit of analysis to avoid duplication of nonbilateral data.

Predictor variables

Minimum and fixed location JSW measurements for the medial compartment and fixed location JSW measurements for the lateral compartment from radiographs that were obtained under the standardized fixed flexion acquisition protocol (http://oai.epi-ucsf.org/datarelease/operationsManuals/RadiographicManual.pdf) were colle cted from the OAI database. Minimum quantitative JSW and fixed location JSW were measured for the OAI using an automated software method[12,13]. Minimum JSW from the OAI was defined as the minimum distance between the femur and tibia in the medial tibiofemoral compartment. In fixed location JSW measurements, the distance between the femur and tibia was measured at fixed intervals in the medial and lateral compartments. In the current study, the variable quantitative minimum JSW represented the lowest fixed interval measurement made from the medial or lateral compartment. The predictor variables of primary interest were baseline quantitative minimum JSW and 4-year change in minimum JSW (JSN). The 4-year JSN was calculated by subtracting the baseline minimum JSW from the minimum JSW at 4 years after enrollment. This analysis was repeated for the most responsive JSW at $x = 0.275$. To control for potential confounding, several covariates were included in the analyses based on previous literature[14,15]. These included age, gender, body mass index (BMI), race, knee alignment, and baseline measures of the 4-year outcome of interest. OAI variable names for the predictor variables used were V00AGE, P02SEX, P01BMI, P02RACE, V00rkdefcv, V00RKALNMT, V00KOOSKPR, V00KOOSYMR, V00KOOSQOL, V00KOOSFSR, V00CSTIME1, and V0020MPACE.

Outcome measures

Six clinical outcome measures were selected from the OAI database and were categorized as either patient-reported outcomes or performance measures. The patient-reported outcomes were KOOS Pain, Symptom, Quality of Life, and Function, Sports, and Recreation scores measured 4 years after enrollment. KOOS scores range from 0 to 100. A score of 0 represents extreme knee problems, 100 represents no knee problems, and a score change of eight represents the minimum perceptible clinical improvement[7]. The performance measures were 20-m walk pace and time to perform five chair stands measured 4 years after enrollment. OAI variable names for the outcome variables used were V06KOOSKPR, V06KOOSYMR, V06KOOSFSR, V06KOOSQOL, V06CSTIME1, and V0620MPACE.

Statistical analysis

To test for significant differences between all patients and patients included in the analysis, two-tailed two-sample student's t tests with equal variances or two-proportion z tests were performed. To estimate the effect of multiple predictors on outcomes, multiple linear regression modeling was performed using the statistical software package JMP 9 (SAS Institute, Cary, NC). Each model consisted of one outcome measure, nine predictor variables, and two interaction product terms. The nine predictor variables consisted of four demographic variables, two alignment variables, one baseline measure of the outcome of interest, and two JSW variables. Two cross product terms to account for potential interaction were 4-year JSN multiplied by baseline JSW and 4-year JSN multiplied by alignment. The assumptions of normality and constant variance of residuals and independence between observations were met. Effect tests using the f-ratio were used to test for statistical significance of each variable in the models. An α level of 0.05 was used in evaluating significance in Table I. An α level of 0.01 was used to evaluate statistical significance in the multiple linear regression model. A significance level of 0.01 was chosen to reduce the risk of a Type 1 error as a result of performing six regressions.

Results

Patient characteristics

Descriptive statistics for each predictor can be found in Table I. Hypothesis testing was performed comparing means between all patients (n = 1,278) and patients included in analysis (n = 942).

Table I
Descriptive statistics for predictor variables

	All patients ($n = 1278$)			Patients included in analysis with all data points ($n = 942$)			*P*-value
	Mean (SD)	Median (Min, Max)	Count (%)	Mean (SD)	Median (Min, Max)	Count (%)	
Baseline age	61.3 (9.1)	61 (45, 79)		61.2 (9.1)	61 (45, 79)		0.65
Gender							
Male			565 (44.2)			442 (46.9)	0.21
Female			713 (55.8)			500 (53.1)	0.21
Baseline BMI	30.2 (4.9)	29.7 (18.2, 48.7)		29.8 (4.7)	29.5 (18.2, 48.7)		0.11
Race							
White or Caucasian			915 (71.6)			705 (74.8)	0.09
Black or African American			325 (25.4)			211 (22.4)	0.10
Asian			11 (0.9)			7 (0.7)	0.60
Other non-white			27 (2.1)			19 (2.0)	0.87
Baseline alignment							
Valgus			524 (41.6)			393 (41.7)	0.96
Varus			380 (30.1)			304 (32.3)	0.27
Neither			357 (28.3)			245 (26.0)	0.23
Baseline alignment, degrees (valgus negative)	−0.47 (4.08)	0 (−22, 15)		−0.33 (4.04)	0 (−22, 15)		0.40
Baseline KOOS pain score	73.5 (19.2)	75 (3, 100)		75.1 (18.7)	78 (6, 100)		0.04
Baseline KOOS symptoms score	77.6 (17.1)	82 (21, 100)		79.2 (16.2)	82 (21, 100)		0.03
Baseline KOOS quality of life score	51.5 (19.4)	50 (0, 100)		52.9 (18.5)	56 (0, 100)		0.09
Baseline KOOS function, sports, and recreational activities score	53.9 (26.1)	50 (0, 100)		55.2 (25.6)	55 (0, 100)		0.32
Baseline repeated chair stands (seconds. hundreths)	13.06 (4.79)	12.14 (4.00, 53.13)		12.83 (4.57)	12.03 (5.09, 48.57)		0.29
Baseline 20-m walk: pace (m/sec)	1.27 (0.22)	1.28 (0.24, 1.96)		1.29 (0.21)	1.29 (0.56, 1.96)		0.12
Baseline minimum JSW [mm]	3.58 (1.54)	3.8 (0.0, 7.9)		3.73 (1.46)	3.9 (0.0, 7.7)		0.02
4-year JSN [mm]	−0.55 (0.94)	−0.4 (−5.2, 3.9)		−0.54 (0.94)	−0.4 (−5.2, 3.9)		0.90

α level = 0.05.

Both groups showed no statistically significant difference in all predictors except baseline KOOS Pain score, baseline KOOS Symptom score, and baseline minimum JSW. The difference in KOOS Pain score and KOOS Symptom score was 1.6 between both groups. With a threshold for clinical significance at a KOOS score of 8, these differences were not clinically significant. The difference in baseline minimum JSW between groups was 0.15 mm. With a threshold for the smallest detectable difference in quantitative JSW being 0.2 mm, this difference was not clinically significant[6].

Regression modeling

Table II shows the results of predictor variables in each of the six multiple linear regression models created. Additional information on parameter estimates and confidence intervals for each model can be found in Supplemental Tables 1–6. Baseline measures of the outcome of interest were significantly correlated with the 4-year outcome in all six models. For example, a better baseline KOOS Pain score significantly correlated with a better 4-year KOOS Pain score. Lower minimum baseline JSW and a negative 4-year JSN were correlated with significantly worse 4-year KOOS Pain, Symptom, and Quality of Life scores. There were no significant correlations between minimum baseline JSW or 4-year JSN and 4-year KOOS Function, Sports, and Recreation scores and performance measures. Repetition of these analysis for JSW at $x = 0.275$ showed similar results (Supplemental Table 7).

Table III displays model parameter estimates and changes in the variable needed to cause a clinically significant eight-point decrease

Table II
Predictor variables and model results

Variable	4-year KOOS measures, *P*-values				4-year performance measures, *P*-values	
	Pain	Symptom	Function, Sports, and recreation	Quality of life	20-m walk pace (m/sec)	Repeated chair stands time (sec)
Baseline value of the 4-year outcome	<.0001*	<.0001*	<.0001*	<.0001*	<.0001*	<.0001*
Baseline minimum JSW [mm]	<.0001*	<.0001*	0.1086	0.0011*	0.0174	0.9402
4-year JSN [mm]	<.0001*	<.0001*	0.0223	0.0022*	0.1986	0.7749
Baseline age	0.0208	0.0002*	0.8286	0.002*	<.0001*	<.0001*
Gender	0.7298	0.6797	0.3737	0.9521	0.2476	0.9228
Baseline BMI	0.0775	0.3986	0.4076	0.0879	0.0002*	0.0204
Racial background	0.0062*	0.0563	0.8281	0.3495	<.0001*	0.0692
Baseline alignment	0.0426	0.37	0.1293	0.5085	0.7171	0.1859
Baseline alignment, degrees (valgus negative)	0.9426	0.7799	0.2579	0.6794	0.953	0.1998
(Baseline minimum JSW) × (4-year JSN)	0.4598	0.5705	0.3093	0.3138	0.1717	0.1105
(Baseline alignment) × (4-year JSN)	0.0022*	0.0817	0.7061	0.0877	0.9281	0.2
Model R^2	**0.346**	**0.356**	**0.354**	**0.319**	**0.557**	**0.290**

* Indicates *P*-value <0.01 for the *F*-test of each variable.

Table III
Variable values associated with a clinically significant change in 4-year KOOS outcome

Variable	4-year KOOS outcome					
	Pain		Symptom		Quality of life	
	Parameter estimate (95% CI)	Change associated with eight-point decrease in KOOS	Parameter estimate (95% CI)	Change associated with eight-point decrease in KOOS	Parameter estimate (95% CI)	Change associated with eight-point decrease in KOOS
Baseline value of the 4-year outcome	0.49 (0.43, 0.54)	−16.43	0.51 (0.45, 0.57)	−15.64	0.59 (0.53, 0.66)	−13.46
Baseline minimum JSW [mm]	1.94 (1.19, 2.69)	−4.13	1.66 (1.01, 2.32)	−4.81	1.42 (0.57, 2.27)	−5.63
4-year JSN [mm]	2.31 (1.18, 3.44)	−3.46	2.56 (1.57, 3.54)	−3.13	2.03 (0.73, 3.32)	−3.95

in KOOS outcome scores. Data from the statistically significant predictors has been summarized for 4-year KOOS Pain, Symptom, and Quality of Life outcomes. With all other predictors constant, a 4.1, 4.8, and 5.6 mm lower baseline JSW resulted in an eight-point drop in 4-year KOOS Pain, Symptom, and Quality of Life scores, respectively. Additionally, a 3.5, 3.1, and 4.0 mm decrease in 4-year JSN resulted in an eight-point drop in 4-year KOOS Pain, Symptom, and Quality of Life scores, respectively.

Discussion

Our results indicate that quantitative JSW measurements are associated with 4-year clinical outcomes in knee OA. With all other predictors held constant, lower minimum baseline JSW and a more negative 4-year JSN were significantly ($P < 0.01$) correlated with worse 4-year KOOS Pain, Symptom, and Quality of Life scores. Baseline JSW and 4-year JSN did not significantly ($P < 0.01$) correlate with performance measures at the 4-year time point. Walking pace and repeat chair stand time may not be sensitive enough to be predicted by joint space changes. Interestingly, patients with narrower joint spaces at the onset of study had worse KOOS Pain, Symptom, and Quality of Life scores at 4 years even after controlling for 4-year JSN and baseline KOOS scores. These data suggest that the joint status of the knee at the outset of the study is as correlated with future clinical outcomes as the degree of JSN over time for this cohort of patients. The 4-year KOOS Pain score was most sensitive to changes in the baseline JSW. A 1 mm lower baseline JSW corresponded to a 1.94 point worsening in 4-year KOOS Pain.

Combinations of the predictors also correlated with clinically significant eight-point changes in the KOOS outcome measures. For example, a 65-year-old white female patient with a BMI of 28, varus alignment, baseline KOOS Pain score of 73, baseline JSW of 3.5 mm, and 4-year JSN of 0.5 mm would be predicted to have a KOOS Pain score of 81.4 in 4 years. In contrast, a 65-year-old white male with a BMI of 28, valgus alignment, baseline KOOS Pain score of 73, baseline JSW of 2.5 mm, and 4-year JSN of 1 mm would be predicted to have a KOOS Pain score of 73.1 in 4 years. This represents a clinically significant difference of 8.3 in the KOOS Pain score as a result of minor changes in the patient characteristics.

Our study displays the associative value of radiographic quantitative JSW measurements at baseline and radiographic JSN over 4 years. Using multiple linear regression analysis, we found lower radiographic measurements correlated with worse KOOS Pain, Symptom, and Quality of Life outcome scores 4 years later. Previous studies have also found a correlation between radiographic changes and clinical symptoms[16–19]. A longitudinal study by Fukui *et al.* concluded that worse symptoms measured via the Japanese Knee Osteoarthritis Measure were significantly correlated with higher rates of JSN[16]. Duncan *et al.* reported a cross-sectional analysis concluding that radiographic OA measured via Kellgren and Lawrence (KL) grading correlates with pain, stiffness, and disability measured via Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index scores[17]. Analyzing data from the MOST and Framingham studies, Neogi *et al.* found a correlation between knee pain and radiographic OA measured via KL grading when comparing two knees within a person[18]. KL radiographic grading was also correlated with knee pain in a within-person comparison of the Health, Aging, and Body Composition study[19]. These studies contradict the discordance between radiographic and clinical OA found in systematic reviews[9,10,20,21]. Our study, in agreement with studies finding an association, indicates a correlation between radiographic and clinical OA.

KL grading, however, is not best suited for measurement of disease progression because it is observer dependent, mixes multiple pathologic changes onto one scale, and is not linear[6]. By using a continuous quantitative JSW measurement and 4-year longitudinal data with a large nationwide study sample, we have shown the correlation between baseline radiographic measurements for progression and standardized KOOS clinical outcome measures. The prediction of disease progression is central in a patient care perspective. Previous studies have shown that knees with worse initial radiographic KL grades were more likely to worsen radiographically over time[22,23]. We have shown worse initial JSW measurements lead to worse clinical outcomes over time after adjusting for multiple confounding variables. Baseline JSW remains independently correlated with worse KOOS outcome scores even after 4-year JSN and baseline KOOS scores were adjusted for in the multiple linear regression. These results suggest that once the disease process has begun the clinical outcome is predetermined to an extent. Therefore, it may be necessary to begin disease modifying OA therapies in an early stage of disease. As baseline JSW is independently associated with 4-year clinical outcomes, it could be used as an early surrogate marker for the effectiveness and benefit of prior disease modifying therapy over a longer time course. Radiographic JSW changes may manifest before clinically important outcomes in knee OA. Future studies looking at the impact of early JSW changes (e.g., loss over 1–2 years) on the progression of OA signs and symptoms could provide a means of targeting potentially vulnerable patient populations early on. Treating these patients with disease modifying agents and measuring clinical outcomes could show slowing, stabilizing, or even reversal of disease progression over time.

There are several limitations in this study. The study population included only individuals with symptomatic and radiographic OA at the onset. Future studies should assess the predictive value of structural JSW measures in patients with earlier OA and asymptomatic patients who progress to symptomatic OA. The right knee was chosen in all patients to avoid subjectively choosing KL grade or KOOS Pain score to judge which knee was most diseased when a large proportion of patients' knees could not be differentiated in this way. Only one knee per patient was used for analysis to avoid

dependence in the data which is required during multiple linear regression analysis however, the right knee may not have been the most symptomatic knee in each patient. Attempting to correlate radiographic data of an individual knee with global patient outcome data may have decreased the correlation between JSW and select outcomes. While outcome measures for KOOS Pain and Symptoms were reported uniquely for each knee, KOOS Quality of Life, KOOS Function, Sports, and Recreation, and performance measures were reported for the patient not each knee. Additionally, there is the possibility that patients were able to perform the 20-m walk and chair stands at a higher level than typical for a brief period of time despite negative joint changes. These factors could explain why a statistically significant correlation was not found for KOOS Function, Sports, and Recreation scores and performance measures. A systematic review by Dobson *et al.* concluded the timed up and go test and multi-activity measures like the Stratford battery, the Physical Activity Restrictions, and Functional Assessment System were part of the best rated performance measures in lower limb OA[24]. These performance measures could be more sensitive to changes in JSW and warrant future evaluation.

Our study included minimum JSW measurements of either the medial or lateral compartments of the knee to assess narrowing throughout the knee joint. Analysis of the data using only medial compartments yielded similar results (data not shown). Analysis of fixed location JSW in the medial compartment was also conducted by comparing the lowest fixed location JSW at baseline with the same location after 4 years. The analysis yielded similar results for all of the models except for the KOOS Quality of Life model: baseline JSW ($P = 0.031$) and 4-year JSN ($P = 0.023$) were no longer statistically significant predictors ($P < 0.01$) of 4-year KOOS Quality of Life scores (data not shown). Fixed location JSW showed less change over time compared to minimum JSW.

In conclusion, our results indicate that quantitative joint space measurements are significantly correlated with 4-year clinical outcomes in knee OA. The results show that a lower initial JSW and a larger 4-year decrease in JSW are both independently associated with worse KOOS Pain, Symptom, and Quality of Life scores after 4 years. The strong association is one feature in knee OA supporting a causative role between structural OA and clinical outcomes. As patients with narrower JSW at the onset of study had worse clinical outcomes after 4 years, any therapeutic intervention would be most beneficial if treatment is targeted as early as possible in the disease process.

Contributions

Sameer R. Oak: Conception and design, collection and assembly of data, analysis and interpretation of data, drafting of the article, final approval of the article.

Anish Ghodadra: Conception and design, critical revision of the article, final approval of the article.

Carl S. Winalski: Conception and design, critical revision of the article, final approval of the article.

Anthony Miniaci: Conception and design, critical revision of the article, final approval of the article.

Morgan H. Jones: Conception and design, analysis and interpretation of data, critical revision of the article, final approval of the article.

Role of the funding source

The funding sources had no role in the design, analysis, and interpretation of data.

Competing interests

The authors have no competing interests that influenced this manuscript.

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Supplementary data

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References

1. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010 Aug;26(3):355–69.
2. Murphy L, Schwartz TA, Helmick CG, Renner JB, Tudor G, Koch G, *et al*. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 2008 Sep 15;59(9):1207–13.
3. Wright EA, Katz JN, Cisternas MG, Kessler CL, Wagenseller A, Losina E. Impact of knee osteoarthritis on health care resource utilization in a US population-based national sample. Med Care 2010 Sep;48(9):785–91.
4. Murphy L, Helmick CG. The impact of osteoarthritis in the United States: a population-health perspective: a population-based review of the fourth most common cause of hospitalization in U.S. adults. Orthop Nurs 2012 Apr;31(2):85–91.
5. Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011 Jun 18;377(9783):2115–26.
6. Hunter DJ, Le Graverand M-PH, Eckstein F. Radiologic markers of osteoarthritis progression. Curr Opin Rheumatol 2009 Mar;21(2):110–7.
7. Roos EM, Lohmander LS. The knee injury and osteoarthritis outcome score (KOOS): from joint injury to osteoarthritis. Health Qual Life Outcomes 2003 Nov 3;1(1):64.
8. Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, *et al*. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. Osteoarthr Cartil 1996 Dec;4(4):217–43.
9. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord 2008 Sep 2;9:116.
10. Kinds MB, Welsing PMJ, Vignon EP, Bijlsma JWJ, Viergever MA, Marijnissen ACA, *et al*. A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. Osteoarthr Cartil 2011 Jul;19(7):768–78.
11. Nevitt M, Felson D, Lester G. The Osteoarthritis Initiative: Protocol for the Cohort Study [Internet] 2006. Available from: http://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf.
12. Duryea J, Li J, Peterfy CG, Gordon C, Genant HK. Trainable rule-based algorithm for the measurement of joint space width in digital radiographic images of the knee. Med Phys 2000 Mar;27(3):580–91.

13. Neumann G, Hunter D, Nevitt M, Chibnik LB, Kwoh K, Chen H, *et al*. Location specific radiographic joint space width for osteoarthritis progression. Osteoarthr Cartil 2009 Jun;17(6):761–5.
14. Hunter DJ. Risk stratification for knee osteoarthritis progression: a narrative review. Osteoarthr Cartil 2009 Nov;17(11):1402–7.
15. Wolfe F, Lane NE. The longterm outcome of osteoarthritis: rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis. J Rheumatol 2002 Jan;29(1):139–46.
16. Fukui N, Yamane S, Ishida S, Tanaka K, Masuda R, Tanaka N, *et al*. Relationship between radiographic changes and symptoms or physical examination findings in subjects with symptomatic medial knee osteoarthritis: a three-year prospective study. BMC Musculoskelet Disord 2010;11:269.
17. Duncan R, Peat G, Thomas E, Hay E, McCall I, Croft P. Symptoms and radiographic osteoarthritis: not as discordant as they are made out to be? Ann Rheum Dis 2007 Jan;66(1):86–91.
18. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, *et al*. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. BMJ 2009;339:b2844.
19. Javaid MK, Kiran A, Guermazi A, Kwoh CK, Zaim S, Carbone L, *et al*. Individual magnetic resonance imaging and radiographic features of knee osteoarthritis in subjects with unilateral knee pain: the health, aging, and body composition study. Arthritis Rheum 2012 Oct;64(10):3246–55.
20. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000 Jun;27(6):1513–7.
21. Dieppe PA, Cushnaghan J, Shepstone L. The Bristol "OA500" study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. Osteoarthr Cartil 1997 Mar;5(2):87–97.
22. Felson D, Niu J, Sack B, Aliabadi P, McCullough C, Nevitt MC. Progression of osteoarthritis as a state of inertia. Ann Rheum Dis 2013 Jun;72(6):924–9.
23. Leyland KM, Hart D, Javaid MK, Judge A, Kiran A, Soni A, *et al*. The natural history of radiographic knee osteoarthritis: a fourteen-year population-based cohort study. Arthritis Rheum 2012 Jul;64(7):2243–51.
24. Dobson F, Hinman RS, Hall M, Terwee CB, Roos EM, Bennell KL. Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. Osteoarthr Cartil 2012 Dec;20(12):1548–62.